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to contain a higher percentage of potentially relevant molecules. The skills of computational chemists have been employed to design such compound libraries for testing.

Two type of libraries were considered possible: first, a library which explored the diversity of structures in chemical space across the range of compounds which could be synthesized without oversampling the same area of diversity space (redundant testing); and second, a library in which the compounds would be likely to have the same biological activity as a known molecule or drug. The major problem confronting computational chemists in the selection of compounds for such libraries was how to characterize the compounds in a manner which would permit the desired selections. Bioscientists have long known that the three dimensional shape of a compound which acts as a ligand to a larger biomolecule must be complimentary to the shape of the binding site of the larger biomolecule. In studying the relationships between the chemical structure of a molecule and its biological activity (structure activity relationships-([SAR]) many techniques to characterize the three dimensional shape of molecules were devised. One of the most successful of the techniques for generating a quantitative structure activity relationship (QSAR) characterized the shape of molecules by defining an interaction energy field between a probe molecule and each part of the studied molecule in a three dimensional grid surrounding the molecule. The shape data thus generated for a series of molecules could be correlated with the biological activity of the molecules to produce the QSAR. This technique by Cramer and Wold (Comparative Molecular Field Analysis [CoMFA]) is described in detail in U.S. Patent No.5,025,388 and U.S. Patent No. 5,307,287.

Use of the CoMFA approach required detailed considerations of two major factors: 1)